

EXHIBIT K

FREE

Meeting Abstract | June 2013

Anti-VEGF Gene Therapy for Wet AMD: Safety and Tolerability of Subretinal Delivery in a Phase I/II Clinical Trial

Ian Constable; Cora Pierce; Sendhil Somasundaram; May Lai; Thomas Chalberg; Mark Blumenkranz; Richard Samulski; Elizabeth Rakoczy

+ Author Affiliations & Notes

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Abstract

Purpose: To evaluate the safety and tolerability of extrafoveal, subretinal injection in elderly patients for the delivery of an anti-VEGF gene therapy agent for wet age-related macular degeneration (wAMD).

Methods: One week after injection with ranibizumab, subjects underwent standard pars plana vitrectomy (PPV) followed by subretinal injection of 100 microliters of therapeutic agent. Subjects could elect either general (GA) or local (LA) anesthesia. Subretinal injection was performed using a commercially available 41g cannula, and documented using a high-definition AJA Ki Pro video system. The adeno-associated viral vector construct rAAV.sFlt-1 was designed to confer multiyear local production of sFlt-1, a potent, naturally occurring anti-VEGF protein. Local and systemic safety parameters were assessed in 12 treated plus 5 control subjects. Control patients had ranibizumab injections on an extend program with monthly OCT review.

Results: The mean age of patients was 79 years and the cohort had a wide range of pre-existing age-related diseases. Four patients had GA and 8 had parabulbar LA only. Vitrectomy was performed and posterior vitreous detachment (PVD) was confirmed in all patients. The therapeutic agent was delivered via a 41 G retinotomy in the superior retina near the vascular arcades, adjacent to but not including the

EXHIBIT K

fovea. Delivery was successfully documented in all 12 subjects. The induced bleb was transient, able to be visualized clinically and via optical coherence tomography (OCT) at 2 hours, but invisible by 24 hours post injection. There were no serious surgical complications such as endophthalmitis, retinal tears, or detachments. All subjects tolerated the procedure well. There was no evidence of local or systemic toxicity. Adverse events were minor, not visually significant, and consistent with standard vitrectomy with PVD induction. No drug-related adverse events were observed.

Conclusions: PPV with extrafoveal subretinal injection is a straightforward procedure that is compatible with parabolbar LA. Whereas a similar approach has been used for children and young adults undergoing gene therapy for retinal dystrophy, we show here that subretinal injection is well-tolerated by elderly patients with wAMD. Transfection of the retinal cells with subretinal rAAV.sFlt-1 may provide a promising strategy for long-term anti-VEGF therapy following a single procedure.

Keywords: 762 vitreoretinal surgery • 412 age-related macular degeneration • 538 gene transfer/gene therapy

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